B6 98. **Amended** A method for [modulating] inhibiting responsiveness in an anergic T cell, comprising contacting said T cell with an agent which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is [modulated] inhibited.

REMARKS

Claims 48-101 were pending in the application. Applicants hereby affirm election of the Group II invention (claims 48 and 71-98). Accordingly, claims 49-70 and 99-101, drawn to non-elected inventions, have been canceled without prejudice for further prosecution in one or more divisional applications. Claims 71, 76, and 92 have also been canceled and claims 48, 72, 77, 82, 83, 89, 97, and 98 have been amended to recite the correct dependencies. Accordingly, claims 48, 72-75, 77-91, and 93-98 are currently pending and all are believed to be directed to the elected invention.

At paragraph 3 of the pending Office Action, the Examiner has argued that the title of the specification is not descriptive and has requested the submission of a new title. Accordingly, Applicants have amended the title of the specification to clearly indicate the invention to which the presently pending claims are directed. Applicants submit that the amendments to the specification are sufficient to overcome the Examiner's objections to the disclosure and respectfully request that these objections be withdrawn.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s). For the Examiner's convenience the pending claims are set forth in Appendix A.

Rejection of Claims 48 and 71-98 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 48 and 71-98 under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to use the invention."

A. The Specification Enables the *in Vivo Use of* Cytokine Receptor γ Chain-Specific Antibodies or other Agents to Inhibit T Cell Responsiveness

The Examiner is of the opinion that "Applicant has not disclosed how to use cytokine receptor γ chain-specific antibodies to inhibit T cells therapeutically commensurate in scope with claimed methods" and that "[t]here is insufficient information or nexus of the invention with respect to the in vivo ability of cytokine receptor γ chain-specific antibodies to inhibit T cell responsiveness, particularly in vivo, to use applicant's invention." It is further the Examiner's position that

> Applicant's disclosure does not provide any objective evidence of either in vitro, ex vivo or in vivo inhibition of T cell responses with cytokine receptor γ chain-specific antibodies. Further, it is noted that the non-elected claims recite using cytokine receptor γ chain-specific antibodies to achieve the opposite effect of stimulating T cells. It is noted that the instant inventor has disclosed that the same or similar description disclosed in the instant specification provides some evidence that after T cell receptor signaling, an event mediated through the γ_c prevents the induction of anergic state, yet this analysis only helps to begin to decipher the molecular mechanism associated with T cell anergy (Boussiotis et al. Science, 1994; 1449, #AJ; see last paragraph).

Moreover, the Examiner argues that "[i]n vitro and animal model studies have not correlated well with in vivo clinical trial results in patients" and that "[s]ince the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the disclosure as filed accurately reflects the relative efficacy of the claimed therapeutic strategies." The Examiner believes that

> [p]harmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivate before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The Examiner also argues that "applicant's methods encompass targeting both acute and chronic inflammatory conditions" and that

> [a]lthough in vitro experiments and animal models can validate concepts based on studies of human disease, such studies are limited to the acute as opposed to the chronic nature of the disease. For example, in animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Therefore, reliance on the examples of experimental protocols wherein cytokine receptor γ chain-specific antibodies administered at the same time as an inflammatory stimulus may inhibit T cell responses (e.g. acute graft rejection); such results may not reflect targeting those chronic diseases (e.g. autoimmunity, allergy) encompassed by the claimed methods. Immunosuppression is much easier to achieve under such controlled conditions to defined antigens under controlled conditions than that experienced in the human immunoregulatory diseases targeted by the claimed invention. Again, no objective evidence of inhibitory cytokine receptor γ chain-specific antibodies in systems predictive of the therapeutic methods encompassed by the claimed invention has been presented.

The above quoted rejection of claims 48 and 71-98 is respectfully traversed on the grounds that the present specification does provide adequate guidance which would enable the ordinarily skilled artisan to make and use the claimed invention. First, it is respectfully submitted that the relevant question is whether the specification "adequately teaches one of ordinary skill in the art how to make or use ***the claimed invention***." It is not necessary for Applicants to provide *in vivo* data as to whether the method of the instant invention can be used

for the treatment of human disease, but rather Applicants must adequately teach the ordinarily skilled artisan how to make or use the claimed invention, e.g., use the methods being claimed.

The claimed invention in this application, as presently pending, encompasses a method for inhibiting T cell responsiveness. The method includes contacting a T cell which expresses a cytokine receptor γ chain with an agent which inhibits a signal associated with ligation of the cytokine receptor γ chain such that T cell responsiveness is inhibited, and (ii) detecting whether signal transduction via the cytokine receptor γ chain occurs, wherein the agents is selected from the group consisting of an anti-interleukin-4 antibody, an anti-interleukin-7 antibody, and an anti-interleukin-15 antibody.

Applicants respectfully submit that the specification provides a teaching which would enable one of ordinary skill in the art to inhibit T cell responsiveness *in vivo* via the use of cytokine receptor γ chain specific antibodies or other agents. To begin with, sufficient guidance exists in the specification as to the types of γ chain inhibitory agents which can be used and methods for making them. More specifically, starting at page 12, line 30 through page 14, line 1 of the specification, anti-γ chain antibodies, anti-cytokine antibodies in general, peptide fragments, peptide mimetics, and methods for making them are described. Moreover, at page 18, line 1, through page 20, line 6, dosage regiments, as well as routes of administration, and pharmaceutically acceptable formulations for the delivery of these agents *in vivo,* are described.

Further, Applicants disclosure provides specific, working examples demonstrating that stimulation of the common γ chain of the IL-2, IL-4, and IL-7 receptors prevents the induction of anergy in T cells (see Example 2, at pages 22-23 of the specification). Moreover, Example 4, at pages 25-26 of the specification, demonstrates that stimulation of the common γ chain of IL-15 also prevents the induction of anergy in T cells.

The standard for establishing therapeutic utility of biotechnological inventions under 35 U.S.C. § 112, first paragraph, was recently addressed by the CAFC in the case of *In re Brana*, 51 F.3d 1560; 34 U.S.P.Q.2D 1437 (CAFC, decided March 30, 1995). In this case, the CAFC held that

> [a] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.*** In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (CCPA 1971) (emphasis added). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Id. at 224, 169 U.S.P.Q. (BNA) at 370. ***Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.*** See In re Bundy, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (CCPA 1981) (emphasis added).

In summary, the essence of the Court's decision was that if a patent disclosure contains a teaching of how to make and use an invention which is commensurate with the scope of the claims and, further provides specific working examples in support of the stated utility which then further evidence should ***not*** be required to satisfy the enablement requirement of section 112, first paragraph, ***unless there is reason to doubt the objective truth of the statements contained in the disclosure which are relied on for enabling support.*** Applicants submit that the present disclosure fully satisfies the enablement standard set forth in *In re Brana* in that it provides more than a sufficient teaching of how to make and use the claimed invention and further provides working examples demonstrating the *in vitro* efficacy of the claimed invention which, together, render credible the asserted use of the claimed methods for *ex vivo* or *in vivo* treatment of human disease states.

With respect to the Examiner's reliance on Boussiotis et al. (1994) to argue that the mechanism associated with T cell anergy is not known, Applicants respectfully submit that "[a]n inventor need not comprehend the scientific principles behind the invention. The inventor's theory or belief as to how his invention works is not a necessary element to satisfy the enablement requirement" and that "it is not a requirement of patentability that an inventor

correctly set forth, or even know, how or why the invention work." *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), *Newman v. Quigg*, 877 F.2d 1575, 11 USPQ2d 1340 (Fed. Cir. 1989).

In view of the above, the ordinarily skilled artisan would not have been required to use "undue experimentation" to determine how to use a γ chain inhibitory agent, as alleged by the Examiner. Thus, the ordinarily skilled artisan, following a careful reading of the above-described teachings from Applicants' specification can make and use the claimed invention. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection.

B. The Extrinsic Evidence Relied on by the Examiner Fails to Support the Position that In Vitro and Animal Model Studies Have Not Correlated Well With In Vivo Clinical Results

The Examiner relies on several publications to support his assertion that in vitro and animal model studies have not correlated well with in vivo clinical results. The Examiner first relies on Kahan et al. for teaching that "no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol., 1992; see entire document, particularly page 558, column 2)."

Applicants respectfully submit that Kahan's criticism of *in vitro* immune assays is directed to immunosuppressive drugs (pharmacological agents) such as Aza, steroids, CsA, and Fk-506 (see page 558, column 2, a few lines before the sentence quoted by the Examiner), and not to the use of antibodies or other agents which bind, e.g., to the γ-chain of a cytokine receptor. In fact, Kahan et al. describe positive results obtained using animal models some of which were confirmed in humans (see, for example, page 557, column 2, where Stoppa's results are described). Essentially, Kahan et al. describe how Stoppa et al. used a mouse antibody directed against LFA-1 to successfully reverse steroid resistant acute graft versus host reactions in man, after this was tested in an animal model. Thus, Applicants respectfully submit that, in contrast to

the Examiner's assertion, *in vitro* assays, do reasonably predict and correlate with *in vivo* results, as evidenced by the teachings of Kahan et al. cited by the Examiner.

The Examiner further relies on Bach et al. (TIPS, 1993) for disclosing "the art known limitations of treating autoimmune diseases" and for "clearly indicat[ing] that autoimmune disease cannot be considered as a whole and treatment selection must be considered with each disease (page 213, column 3)" and further for teaching "the art-known resistance of autoimmunity to therapeutic intervention (page 215, column 3)."

Applicants respectfully submit that while Bach et al. recognize some of the difficulties in the application of immune therapy in autoimmune diseases, Bach et al. also teach that "[t]he discovery of new immunosuppressive drugs ... and the emergence of immunologically active products (monoclonal antibodies, cytokines, and peptides) has dramatically changed the approach to the problem by showing that a number of diseases ... were ***clinically improved by these agents***" (see page 213, first and second column). Moreover, Bach et al. describe a series of results obtained by immune therapy methods, which they characterize as "***spectacular effects***" (see page 215, the bottom of the first column). Accordingly, Applicants respectfully submit that, in contrast to the Examiner's assertion, Bach et al. teaches the important progress achieved in the field of immune therapy.

The Examiner further argues that Applicants have used the B7:CD28 system to arrive at their results and relies on Blazar et al. (J. Immunol., 1996) for teaching that "issues such as tissue distribution, half-life, affinity and avidity obtained with these various CD28-B7-specific reagents might prove to be highly important in achieving GVHD protection. However, any conclusion regarding the efficacy of CD28/B7 blockade on altering in vivo immune response should be interpreted in light of the type of reagent infused (Blazar see page 3257, column 2, paragraph 10)." More important, the Examiner continues, "it is unlikely that ongoing T cell responses will be susceptible to inhibition by anti-B7 reagents, for example in autoimmune diseases or allergies" and "[t]herefore, it appears that the administration of inhibitors of the CD28-B7 pathway such as CTLA-4 Ig can result in immunosuppression as observed in several

model systems, however even in these systems the timing of CTLA-4 Ig administration relative to the antigenic exposure of the mechanism by which the foreign antigens were introduced into the host (e.g. timing, dose and site) had significant impact on the success of the intervention." The Examiner believes that "[t]here is insufficient evidence on the tissue distribution, half-life, affinity and avidity of cytokine receptor γ chain specific antibodies as inhibitory reagents in vivo or in vitro."

Applicants respectfully submit that, as discussed above, the relevant question is whether the specification "adequately teaches one of ordinary skill in the art how to make or use ***the claimed invention***" namely, whether the specification adequately teaches one of ordinary skill in the art how to inhibiting T cell responsiveness by contacting a T cell which expresses a cytokine receptor γ chain with an agent which inhibits a signal associated with ligation of the cytokine receptor γ chain such that T cell responsiveness is inhibited, and detecting whether signal transduction via the cytokine receptor γ chain occurs, wherein the agents is selected from the group consisting of an anti-interleukin-4 antibody, an anti-interleukin-7 antibody, and an anti-interleukin-15 antibody. Applicants have indicated *supra* that the specification provides a teaching which would enable one of ordinary skill in the art to inhibit T cell responsiveness *in vivo* via the use of cytokine receptor γ chain specific antibodies or other agents.

Moreover, the reference relied on by the Examiner, namely Blazar et al., discloses that "[i]n vivo infusion of CTLA-Ig has been shown to reduce antibody responses to sheep red blood cells (RBCs) in mice, permit acceptance of human pancreatic islet cell xenografts in mice, and reduce or eliminate rejection of rat cardiac allografts" (see page 3815, last paragraph). Therefore, Blazar et al. teach that the use of such agents has been successful.

Given the teachings of Blazar et al and the teachings of the instant specification, described *supra*, it is the Applicants' position that it would require no more than routine experimentation by one of ordinary skill in the art to determine appropriate regimens (e.g., amount, route of administration, time course of administration, and the like) for introducing γ chain inhibitory agents, e.g., anti-γ chain antibodies, *in vivo*. In *Cross v. Iizuka* (753 F.2d 1040

(Fed. Cir. 1985) the court established that the enablement requirements' how-to-use aspect is met when pharmacological activity in an *in vitro* environment is demonstrated and, accordingly, that the ordinarily skilled artisan can determine dosage levels for therapeutic administration without undue experimentation. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 48 and 98 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 48 and 98 under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, it is the Examiner's opinion that

> [c]laims 48 and 98 are indefinite and ambiguous in the use of "modulating T cell responsiveness" and "such that T cell responsiveness is modulated" in the absence of a clear positive or negative biological effect. Modulation is not appropriate because modulation can occur both in positive and negative directions and applicant elected methods of inhibiting T cell responses. Also, the endpoint of stimulating signals are ambiguous in the absence of what i s the intended or desired biological effect.

Applicants respectfully submit that the amendments to claims 48 and 98 are sufficient to overcome this rejection. More specifically, claims 48 and 98 as amended, are directed to a method of ***inhibiting*** responsiveness in an anergic T cell. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

Rejection of Claims 48, 71-74, 77-90, and 93-98 Under 35 U.S.C. § 102(b) and § 103

The Examiner has rejected claims 48, 71-74, 77-90 and 93-98 under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103 as being obvious over Shimamura et al. (U.S. Patent No. 5,582,826). The Examiner relies on Shimamura et al. for teaching "the use

of cytokine receptor γ chain-specific antibodies as an immunosuppressant medicine effective in preventing the rejection of grafts after transplantation and also in treating inflammatory diseases such as allergic disease and autoimmune diseases (see Summary of the Invention and column 3, paragraph 1)." In particular, the Examiner argues that

> [t]he claimed functional limitations addressed by the application would be inherent properties of the referenced cytokine receptor γ chain-specific antibodies to treat the same inflammatory conditions encompassed by the claimed methods. Although the reference is silent about the mechanism of action of cytokine receptor γ chain-specific antibodies such as its effects on JAK3 kinase, the reference clearly teaches the use of the same cytokine receptor γ chain-specific antibodies to inhibit the same T cell response encompassed by the same therapeutic modalities as applicant. Also see Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

The Examiner further argues that

> [a]lthough the reference clearly teaches inhibiting T cell responses associated with transplantation, it is silent about allogenic, xenogeneic and bone marrow cells as well as GVHD, such limitations would have been either anticipated or obvious to the ordinary artisan in the use of T cell inhibitory antibodies, which were commonly used in such therapeutic regimens at the time the invention was made. Similarly, the reference appears to be silent about alloantigen or autoantigen, however such limitations would have been anticipated or obvious in view of inhibiting T cell responses in the treatment of autoimmunity and transplantation at the time the invention was made.

Therefore, the Examiner concludes, "the instant claims relying upon inhibiting T cell responses as well as the mechanism of action of inhibitory cytokine γ chain-specific antibodies (claims 71-74, 77-85, 88, and 98) are anticipated by the reference." The Examiner is of the opinion that the "use of inhibitory cytokine receptor γ chain-specific antibodies in the treatment of GVHD would either be immediately envisaged in the inhibition of T cell responses in transplantation as taught by the reference or would have been obvious to the ordinary artisan, since the use of such inhibitory antibodies was known and practice at the time the invention was

made (claims 86, 89-97)" and that "the mechanism of action is recited in these claims associated with bone marrow transplantation (see claims 93-96), however these limitations are met by using the same inhibitory cytokine receptor γ chain-receptor antibodies to be used for the same purpose as the claimed invention."

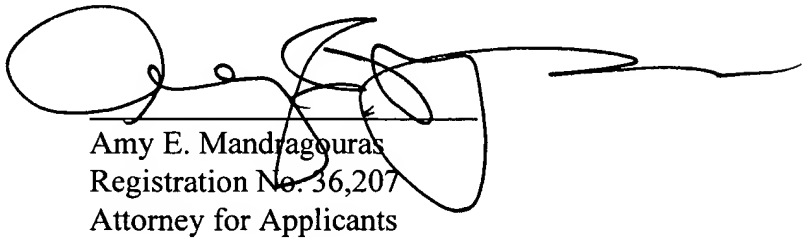
For the purpose of expediting prosecution, Applicants have amended the claims and hereby elect species (iii) within previously elected Group II for further prosecution.

The presently pending claims encompass species (iii) and (iv) but no longer encompass the previously elected species (i) (anti-gamma chain antibody). The art rejections of record do not pertain to the claims as newly amended. Applicants gratefully acknowledge the Examiner's statement that the species of Group II are patentability distinct. The amendments to the claims are being made for the purpose of expediting prosecution and should not be construed as an acquiescence to the Examiner's rejections. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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